## REMARKS

Favorable consideration and allowance are respectfully requested for currently pending claims 1-28 in view of the foregoing amendments and following remarks.

Paragraph [0035] of the specification is amended as provided on page 2 of this paper.

The rejection of claims 1-28 on the ground of nonstatutory obviousness-type double patenting over claims 1-12, 16-23, 41 and 42 of U.S. Patent No. 6,550,701 (the '701 patent) is respectfully traversed.

The present claims relate to an oral administration unit comprising a first active substance tramadol or a pharmaceutically acceptable salt thereof, and a second active substance diclofenac or a pharmaceutically acceptable salt thereof, wherein the two active substances are present in separate subunits (see claim 1).

The '701 patent relates to a multilayered tablet having a tramadol layer, a diclofenac layer and a separating layer.

The specification indicates that the term "separate subunits" means that the active compounds tramadol and diclofenac are each present in separatelv formulated subunits, such as microtablets, microcapsules, ion-exchange resinates, granules, active substance crystals and pellets (see the publication of present application (US 2004/0115267), paragraphs [0009, 0012 and 0013] as well as claim 9). After formulation of the separate subunits, the subunits of tramadol and diclofenac are admixed to form a common administration unit, for example by packing the subunits into hard gelatin capsules (see the publication of the present application, pages 3-5, Examples 1, 3 and 4) or by compressing the subunits into tablets (application publication, page 4, Example 2).

Therefore, the subject matter of the '701 patent is distinct from the subject matter of the present patent application with respect to four mandatory features disclosed in the '701 patent, namely: (a) the administration form is a multilayered tablet; (b) tramadol is present in a tramadol layer in the multilayer tablet; (c) diclofenac is present in a diclofenac layer in the multilayer tablet; and

(d) the tramadol layer and the diclofenac layer are separated by a separating layer in the multilayer tablet (see the '701 patent, abstract and claim 1).

According to the disclosure of the present application, the subunits comprising tramadol and diclofenac are randomly admixed in the final oral administration unit (e.g., hard gelatin capsules, tablet; see above). In contrast, as is evident from the disclosure of the '701 patent, the tramadol and diclofenac layers which are separated by a separating layer are ordered rather than being randomly distributed in the final multilayer tablet.

These distinct features of the final oral administration unit (ordered vs. random design) affect the release profile of the active compounds. This can be seen by comparing the release profiles of the active substances from the distinct administration units of the present application and the '701 patent. In particular, the dosage forms display distinct release profiles.

The multilayered tablet according to the '701 patent shows a hyperbolic release profile similar to the release of tramadol-HCl from a retarded matrix tablet (see '701 patent, Figure 3 and the related text in column 7). In contrast, the administration unit of the present application shows a sigmoidal release profile similar to that of retard pellets containing tramadol-HCl (see present application, Figure 4 and paragraph [0047]). These distinct release profiles, *i.e.*, hyperbolic vs. sigmoidal release profiles, result from differences in the formulations. While the hyperbolic release profile results from the multilayer tablet ('701 patent, claim 1), the sigmoidal release profile is achieved by formulations having the subunits of the present application (see the present application, claim 1).

To further illustrate the distinct release profiles of diclofenac-Na displayed by the distinct administration units of the present application (such as hard gelatin capsules) and the '701 patent (multilayer tablet), a tabular summary is provided below showing experimental results of the release profile measurements for diclofenac-Na (see '701 patent, pages 3-5, Examples 1-3; and in the present application, pages 3-5, Examples 1-4). The administration units comprised in each case 50 mg diclofenac-Na embedded in a retarded form.

| **Present application** | Released fraction in % (diclofenac) | | | |
|---|---|---|---|---|
| time/min | Example 1 | Example 2 | Example 3 | Example 4 |
| 30 | 0.3 | 0 | --- | --- |
| 120 | 0.3 | 0 | 1 | 0 |
| 240 | 12 | 20 | 39 | 82 |
| 360 | 44 | 40 | 59 | 96 |
| 480 | 71 | 78 | 72 | 99 |
| 600 | 87 | 98 | --- | --- |

| **'701 patent** | Released fraction in % (diclofenac) | | |
|---|---|---|---|
| time/min | Example 1 | Example 2 | Example 3 |
| 30 | 0 | 0 | 0 |
| 120 | 0 | 0 | 0 |
| 240 | 11 | 14 | 15 |
| 360 | 14 | 18 | 31 |
| 480 | 32 | 37 | 50 |
| 600 | 48 | 56 | 72 |

As is evident from the tables, the release profile of diclofenac-Na from the oral administration unit of the present application is significantly different from that of diclofenac-Na from the multilayer tablet of the '701 patent. These differences become especially evident after 480 and 600 minutes. While the percent release of diclofenac-Na from the multilayer tablet after 480 and 600 min is in the range of 32-50% and 48-72%, respectively, the percent release for the oral administration unit of the present application (hard gelatin capsules, tablet) after 480 and 600 min is in the range of 71-99% and > 87%, respectively.

Taken together, the multilayer tablet of the '701 patent and the oral administration unit of the present application exhibit significantly distinct release profiles of the active substances:

- for the multilayer tablet of the '701 patent, a hyperbolic release profile is observed for tramadol-HCI, accompanied by a relatively slow release of diclofenac-Na;
- for the oral administration unit of the present application, a sigmoidal release profile is achieved for tramadol-HCI, accompanied by a relatively fast release of diclofenac-Na.

As a result of the significant differences between the administration units of the '701 patent and the present application, the subject matter of the present application is not obvious over the subject matter of the claims of the '701 patent.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 1-28 under 35 U.S.C. § 103(a) over Raffa (EP 0 546 676 A1) in view of Oshlack *et al.* (6,077,533) is respectfully traversed.

The presently claimed invention relates to an oral administration unit containing the active substances tramadol and diclofenac and/or their respective physiologically compatible salts. Each of the two active substances is present in subunits which are separately formulated in each case, and they are provided in the same administration unit (see paragraph [0002] of the publication of the present application).

One object of the present invention was to provide a new pharmaceutical dosage form for the combined administration of tramadol and diclofenac (see application publication, paragraph [0007]). Another object of the present invention was to combine the two active substances tramadol and diclofenac and/or their respective physiologically compatible salts in a common administration unit without impairing the release profiles of the two active substances or reducing their bioavailability (see application publication, paragraph [0008]).

It was surprisingly discovered that these objects could be realized with an oral administration unit comprising a first active substance tramadol or a pharmaceutically acceptable salt thereof, and a second active substance

diclofenac or a pharmaceutically acceptable salt thereof, wherein the two active substances are present in separate subunits (see application publication, paragraph [0009]).

The results of the release profile measurements unambiguously show that these objects are achieved by the inventive oral administration unit. In particular, Figures 1-4 of the present application show that (a) the inventive oral administration unit (Figures 1 of the present application) displays an improved release profile compared to a conventional matrix tablet (Figure 2 of the present application); (b) the oral administration unit comprising both active substances displays a sigmoidal release profile for tramadol as well as for diclofenac – this is commonly only achieved with retard pellets having only one of the active substances (see Figures 1, 3 and 4 of the present application); and (c) the release rate of the active substances from the inventive oral administration unit is comparable to that of the retard pellets comprising only one active substance, i.e. either tramadol or diclofenac (see, Figures 1, 3 and 4 of the present application).

This evidence, showing that both active substances, diclofenac and tramadol, display a sigmoidal release profile from the oral administration unit of the invention, which is almost identical to the release profiles measured for the pellets containing a single active substance, i.e., either tramadol or diclofenac, proves that the invention oral administration unit does not impair the release profiles of the two active substances.

In contrast, as can be seen from Figure 2, if tramadol-HCI and diclofenac-Na are embedded together in a conventional matrix tablet, the release profile of both active substances is disadvantageous. See paragraph [0045] of the published application. In particular, after 480 min, only approximately 45% of tramadol-HCI and only approximately 10% of diclofenac-Na are released from the conventional matrix tablet (see Figure 2 of the present application). In contrast, after 480 min, 79% of tramadol-HCI and 71 % of diclofenac-Na are released from the invention oral administration units (see Figure 1 and paragraph [0044] of the present application).

Thus, when tramadol-HCI and diclofenac-Na are administered to a patient in combination and without suitable measures, such as separate formulation, to prevent the formation of sparingly soluble compounds (see Figure 2 of the present application), the active substances are not adequately released and thus are not adequately bioavailable for effective patient treatment.

The Office Action offers Oshlack *et al.* as disclosing a multiparticulate product comprising beads of an immediate release active core coated with an extended release coating. The reference actually appears to describe coating inert beads with a powder layer of active ingredient and then providing the beads in an immediate release form or with an extended release coating (abstract).

Oshlack does not describe an oral dosage form where two active ingredients are provided, each in their own subunit, as is presently claimed. Instead, in Oshlack, the active ingredient is sprayed to coat inert beads and either the coated beads are inserted into a gelatin capsule (Example 1-3) or the coated beads are coated a second time with an extended release formulation and then inserted into a gelatin capsule (Examples 4 and 5). Even assuming that Oshlack were modified so that two active ingredients were provided, there is nothing to cause one of skill in the art to provide those two active ingredients in separate subunits. Moreover, on the present record there does not appear to be any reason that one of skill in the art might try to combine two active ingredients in a dosage form such as is taught by Oshlack.

The Office Action admits that Oshlack does not teach the combination of tramadol and diclofenac. As described above, the reference does not appear to teach any combination of active ingredients. Given that Oshlack does not teach the combination of tramadol and diclofenac, the reference also does not disclose or recognize the problem arising from the direct combination of tramadol and diclofenac which is the formation of a sparingly soluble compounds. Further, Oshlack *et al.* provides no information as to the release profile achieved by separately formulating subunits of tramadol and diclofenac or that in such an arrangement the release profile of both substances may be almost identical to

that of formulations containing only one active ingredient, i.e., either tramadol or diclofenac (see above).

Raffa (European Patent EP-B-0 546 676) discloses, for example, that the combination of tramadol-HCl with NSAIDs, such as for example ibuprofen, in a composition ratio of 1:l to 1:200 produces a synergistically enhanced analgesic action. However, tramadol-HCI and diclofenac-Na together form a sparingly soluble compound. It is therefore to be expected that the bioavailability of the two active substances is reduced and higher dosages are required to compensate for this decreased bioavailability (see paragraph [0006] of the present application). Thus, contrary to the synergistic effects described for the combination of tramadol and NSAIDS, the combination of tramadol and diclofenac is actually problematic.

When Raffa considers diclofenac or a pharmaceutically acceptable salt thereof as a possible active ingredient, it does so only in an extensive list of NSAIDs (see Raffa, page 3, line 50 to page 4, line 15). Raffa does not disclose that diclofenac is a preferred active substance for the preparation of a pharmaceutical composition. In contrast, propionic acid derivatives and especially ibuprofen are described as preferred active substances (see, Raffa, page 4, lines 14-15). No examples including diclofenac and/or its pharmaceutically acceptable salt are not disclosed in Raffa (see page 4, line 50 to page 6, line 52, Examples 1-3). Only the selections tramadol-HCl/ibuprofen, tramadol- N-oxide/ibuprofen and 0-desmethyltramadol/ibuprofen are explicitly described (see Raffa, page 4, line 50 to page 6, line 52, Examples).

Raffa does not indicate that the active substances tramadol and diclofenac should be formulated separately to achieve desirable release profiles and bioavailability. Further, Raffa does not even consider the possibility that mixtures of tramadol and diclofenac could lead to poor solubilities for the active substances, thereby resulting in low bioavailability. The inventors of the present application determined, however, that in a conventional tablet comprising the active substances tramadol-HCI and diclofenac-Na, the solubility of both substances diminishes significantly (see present application, Figure 2). Raffa

appears to fail to recognize the problem of the formation of sparingly soluble compounds which arise from the direct combination of tramadol and diclofenac.

Although Raffa teaches the claimed ratio between tramadol and NSAID, the reference fails to recognize the possibility of undesirable solubility effects of tramadol and diclofenac, considering only compositions comprising tramadol material and the NSAID ibuprofen.

Although Raffa teaches that a composition comprising a tramadol material and an NSAID displays synergistic analgesic effects, this teaching does not consider the undesirable solubility effects resulting from merely mixing the active substances tramadol and diclofenac. These undesirable solubility effects lead to an undesirable release profile (compare Figures 1 and 2 of the present application).

Considering the proposed combination of Oshlack et al, and Raffa, one of ordinary skilled in the art would have no way to arrive at the presently claimed invention, where tramadol and diclofenac (or salts thereof) are provided in separate subunits of an oral administration form. To even come close to the claimed invention, the person of skill in the art would have to first select tramadol and diclofenac from among a very large number of possible combinations in Raffa. There does not appear to be any reason to cause one of skill in the art to make this selection. Further, one of ordinary skill in the art would have to modify the teachings of these references so as to formulate each of the tramadol and diclofenac separately. There is nothing to provide one of skill in the art with any suggestion that a separate formulation of tramadol and diclofenac would be any different from a mixed formulation of these ingredients. Much less any indication that it might be necessary to overcome undesirable solubility effects or that separately providing the active ingredients would result in a formulation that avoids the solubility problems and provides very advantageous release profile. To the contrary, the references are completely silent as to the solubility problems that occur from combinations of tramadol with diclofenac.

Even assuming, *arguendo*, that one of skill in the art were for some reason to try the combination of tramadol with diclofenac, absent some recognition of the solubility problems associated with combining tramadol with diclofenac, one of skill in the art would have no reason to do anything but use normal mixtures of these components. Because the references do not provide any recognition of the solubility problems associated with such mixtures, the references do not provide any hint toward the presently claimed oral administration units having the active ingredients in separate subunits.

Thus, if one of skill in the art were for some reason to ignore Oshlack's description of single active ingredient dosage forms and try to combine tramadol with an NSAID in a dosage form as described in Oshlack, given Raffa's description of synergies between tramadol and NSAID's the person of skill in the art would be inclined to provide a combination of tramadol and NSAID together and spray this combination onto a single batch of beads. There is nothing to cause one of skill in the art to go to the trouble of providing the tramadol and NSAID apart in separate subunits, as is required of the present claims.

Thus, the proposed combination of references fails to describe an oral administration unit as claimed where two active substances are provided in separate subunits. Further, the proposed combination of references fails to describe such an oral administration unit with two active substances provided in separate subunits where the active substances are tramadol and diclofenac or salts thereof. Accordingly, the proposed combination of references fails to teach or suggest each and every element of the invention. Moreover, given Oshlack's disclosure of single active ingredient dosage forms, Oshlack is not properly combinable with references that call for multiple active ingredients.

Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

## CONCLUSION

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket No. 029310.50777CP).

Respectfully submitted,

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/Christopher T. McWhinney/
J. D. Evans
Registration No. 26,269

Christopher T. McWhinney
Registration No. 42,875

CROWELL & MORING LLP
Intellectual Property Group
P.O. Box 14300
Washington, DC 20044-4300
Telephone No.: (202) 624-2500
Facsimile No.: (202) 628-8844
JDE:CTM:mdm (3054124)